Optum Rx Drug Pipeline Insights Report™

Winter 2024

Optum Rx®

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From Sumit Dutta, Chief Medical Officer at Optum Rx

Hello, and welcome to this edition of the Optum Rx Drug Pipeline Insights Report.

This issue will highlight three drugs with expected approval dates before the end of first quarter 2024. Each of these drugs are groundbreaking, with novel mechanisms of action or as the first treatment in their segment.

But first, a brief re-cap of some of the activity we saw in 2023. As of Dec. 15, the Food and Drug Administration (FDA) had approved 53 novel drugs in 2023. These included significant new treatments that have been covered in previous reports, such as Leqembi® (lecanemab), for Alzheimer's disease; Elevidys™ (delandistrogene moxeparvovec-rokl) for Duchenne muscular dystrophy; Zepbound™ (tirzepatide), a new GLP-1 drug for weight loss; and Zurzuvae™ (zuranolone), for postpartum depression.

Now, here are the featured drugs for this quarter:

Roluperidone is a novel treatment for negative symptoms associated with schizophrenia.

Sotatercept is a first-in-class treatment for pulmonary arterial hypertension. It would provide an additional treatment option for a disease associated with high levels of sickness and death despite currently available therapies.

Resmetirom is a novel treatment for nonalcoholic steatohepatitis (NASH). There are no approved treatments for NASH, a condition with high prevalence in the U.S.

As always, Optum Rx continuously monitors and evaluates the drug pipeline and will share notable upcoming drug approvals in subsequent editions.

Please refer here for additional technical background and supplemental sources.

Sumit Dutta
Chief Medical Officer, Optum Rx

Contents

[Click to go to page]

Roluperidone (brand name: to be determined)

[Back to Contents]

Expected FDA decision: February 26, 2024

Roluperidone is under review for the treatment of negative symptoms in patients with schizophrenia.

Condition

Schizophrenia is characterized by disruptions in thought processes, emotional responsiveness, and social interactions. There are two major categories of schizophrenia symptoms: **positive** and **negative.** Positive symptoms involve distortions of reality and include hallucinations, delusions, paranoia, and exaggerated perceptions. Negative symptoms may include a loss or decrease in the ability to initiate plans, speak, express emotion, or find pleasure.

The positive symptoms of schizophrenia can typically be managed with antipsychotics, including generic options. However, there are currently no approved therapies for negative symptoms of schizophrenia in the U.S.[1]

Key points

Why this drug matters: Potentially the first approved drug for negative symptoms of schizophrenia. Unique mechanism may reduce risk of some adverse events.

Estimated cost: ~$19,000 per year.

Trial notes: Demonstrated significant improvement vs. placebo. However, trials were limited, with mixed results.

Route of administration: Oral

Manufacturer: Minerva Neurosciences

Schizophrenia is typically diagnosed in the late teen years to early thirties. An estimated 2.8 million adults in the U.S. aged 18 or older experience schizophrenia and related psychotic disorders.

Clinical profile

Most existing antipsychotic drugs work by blocking dopamine receptors in the brain. Dopamine plays a role in mental functions like pleasure, memory, motivation, and mood. Unfortunately, blocking dopamine can both improve and worsen the negative symptoms of schizophrenia.[2]

Unlike other antipsychotics, roluperidone does not block dopamine, thus avoiding its potential negative effects. Instead, it blocks a specific subtype of serotonin receptor (5-HT2A) thought to minimize symptoms of schizophrenia, while also blocking other chemical messengers that regulate the sympathetic nervous system (i.e., the 'fight or flight' response).[3]

Trial results

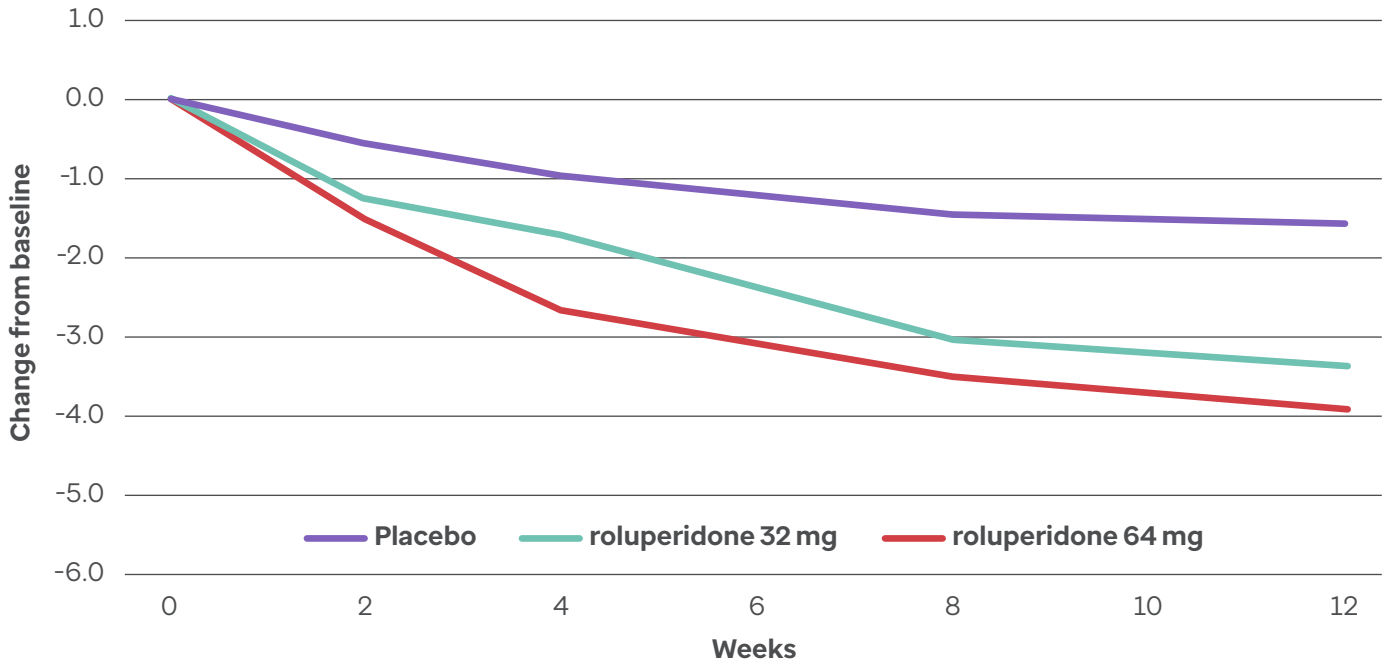
The efficacy of roluperidone was evaluated in one Phase 3 trial and one Phase 2b trial. In both studies, patients were randomized to higher or lower doses of roluperidone, or placebo. Efficacy was measured based on changes in standardized symptom scores at week 12.

- In the Phase 3, symptoms scores 'marginally missed statistical significance' vs. placebo, possibly due to data problems. However, the results for the higher dose roluperidone treatment were 'quantitatively superior' to placebo.[4]
- In the Phase 2b study, both doses of roluperidone **demonstrated** a statistically significant improvement in the standardized score vs. placebo.

Roluperidone *(continued...)*

[Back to Contents]

This graph illustrates the difference between roluperidone and placebo in the Phase 2b study. It tracks changes from baseline measures on a standardized negative symptoms test:



[Image adapted from Minerva Neurosciences. Corporate Presentation. Published January 2022.]

You can access an in-depth discussion of safety and trial data here (p. 5).

Competitive environment

Roluperidone would be the first FDA approved drug for negative symptoms of schizophrenia. Due to its unique mechanism, it may reduce the risk of common adverse events associated with atypical antipsychotics (e.g., weight gain). However, the trial results for roluperidone were mixed, with the lone Phase 3 trial failing to meet its primary endpoint.

In addition to the modest efficacy results, there were several limitations in the pivotal trials that could limit its use in practice. First, it was only evaluated in patients who were stable for their positive symptoms of schizophrenia.

Second, roluperidone was only evaluated as a stand-alone treatment, so it is unknown how the drug would interact with current atypical antipsychotics. Finally, the Phase 2b pivotal study, which did meet its primary endpoint, was conducted exclusively in Europe, so the results may not be generalizable to the U.S. population.

For reference, the Wholesale Acquisition Cost (WAC) for Caplyta® (lumateperone), an atypical antipsychotic available only as a brand, is approximately $19,000 per year.

Sotatercept (brand name: to be determined)

[Back to Contents]

Expected FDA decision: March 26, 2024

Sotatercept is under review for the treatment of adult patients with pulmonary arterial hypertension.

Key points

Why this drug matters: Potential first-in-class treatment, promising efficacy results, high unmet need. Likely reserved as a third- or fourth-line therapy. lack of long-term data

Estimated cost: ~$260,000 per year.

Trial notes: Results appear promising, but studies were limited mainly to treatment-experienced patients. Lacking long-term data.

Route of administration: Subcutaneous injection.

Manufacturer: Merck

Condition

Pulmonary arterial hypertension is a rare, progressive disease characterized by high blood pressure in the arteries of the lungs, making it more difficult for the heart to pump blood to the lungs. Symptoms include shortness of breath, chest pain, fatigue, dizziness, fainting, and swelling in the legs.[5]

The direct medical costs of pulmonary arterial hypertension are estimated at $100,000 per person per year. Eventually, it can lead to premature death — one-fifth of patients die within three years of diagnosis.[6]

Pulmonary arterial hypertension is most common in women between 30 to 60 years old. Approximately 500 to 1,000 new cases are diagnosed each year in the U.S., and it is estimated that 40,000 people are living with the disease.

Clinical profile

Increased blood pressure from pulmonary arterial hypertension is due to an imbalance between cell growth and cells naturally dying at the end of their life cycle.[7] With too many new cells growing, and not enough old cells dying, the result is narrowing blood vessels, thickening of artery walls, and local blood coagulation in the blood vessels of the lungs (i.e., 'vascular remodeling').[8]

Sotatercept works by restoring the proper balance between normal cell growth or facilitating natural cell death, as required.[9] This may help to slow down or even reverse the process of pulmonary vascular remodeling that occurs in pulmonary arterial hypertension.[10]

Trial results

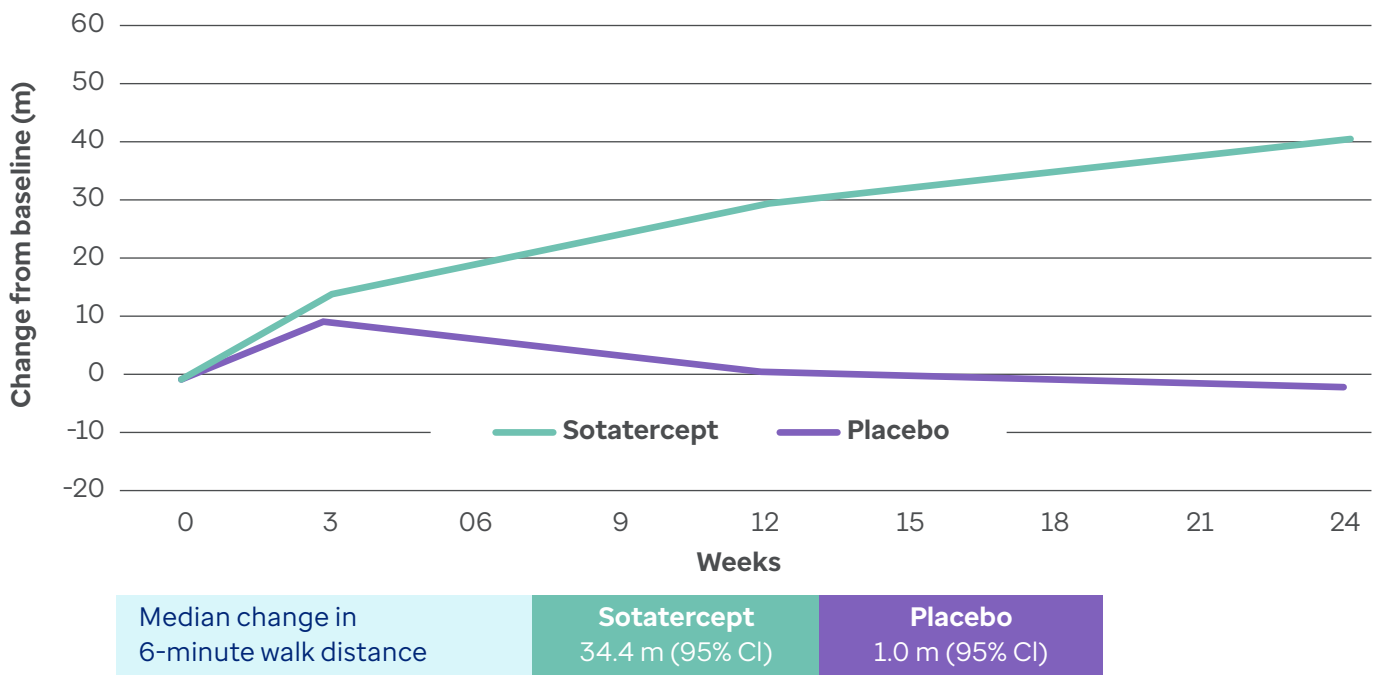
Sotatercept was evaluated in a Phase 3, randomized, double-blind, placebo-controlled study (STELLAR). Patients were randomized to receive sotatercept or placebo every three weeks. The primary endpoint was the change from baseline at week 24 in a standardized activity test (six-minute walk distance). A key secondary endpoint was elapsed time before death or clinical worsening after the last patient completed week 24.

- The median patient in the sotatercept group improved their six-minute walk distance by 34.4 meters at week 24. The placebo group experienced a 1.0 meter improvement over the same period.
- After a median follow-up of 32.7 weeks across the groups, the risk of death or nonfatal clinical worsening events was 84% lower with sotatercept than with placebo.[11]

Sotatercept *(continued...)*

[Back to Contents]

The below graph shows the increase in distance for the 6-minute walk test for patients taking sotatercept vs. placebo:



[Image adapted from New England Journal of Medicine. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. Published April 20, 2023.]

You can access an in-depth discussion of safety and trial data here (p. 7).

Competitive environment

Sotatercept would offer a first-in-class treatment for pulmonary arterial hypertension that could be used in addition to existing treatments. Adding a 24-week treatment with sotatercept to background therapy with currently available medications improved exercise capacity in the six-minute walk test. Additional clinical benefits were also seen across multiple endpoints.[12]

Sotatercept's initial place in therapy will be limited based on the population studied in STELLAR. That population was limited to only patients with specific disease severities and forms of the disease, and with specific forms of pulmonary arterial hypertension. In addition, the overwhelming majority of subjects (95%) were already on dual or triple combination therapy. Also, while the trial results for sotatercept appear promising in treatment-experienced patients, long-term durability of response is still unknown.

Another possible barrier for use is that sotatercept requires subcutaneous injection. Currently, most front-line treatments for pulmonary arterial hypertension are available as oral or inhaled therapies.

For reference, the WAC for Uptravi® (selexipag), a prostacyclin receptor agonist, is approximately $260,000 per year.

Resmetirom (brand name: to be determined)

[Back to Contents]

Expected FDA decision: March 14, 2024

Resmetirom is under review for the treatment of patients with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Key points

Why this drug matters: Potentially the first FDA approved therapy for NASH, large potential target population, appears well tolerated, oral and once daily administration..

Trial notes: Efficacy data is promising, although limited. Long-term outcomes on all-cause mortality, liver transplant, and significant hepatic events not expected until 2025.

Route of administration: Oral, once daily.

Manufacturer: Madrigal Pharmaceuticals

Condition

NASH is a progressive liver disease caused by excessive fat accumulation in the liver that leads to inflammation and liver injury. Progressive liver scarring (fibrosis) can lead to cirrhosis, liver failure, cancer, and death. Additionally, patients with NASH, especially those with other comorbidities (e.g., hypertension, type 2 diabetes), are at increased risk for adverse events such as stroke, heart attack or death.

Today there are approximately 1.9 million people with NASH in the U.S., although the total including those not diagnosed is expected to be much higher. Also, the prevalence of NASH has increased by almost 100% in the past decade. The continued increase of metabolic syndrome in the U.S. is expected to exacerbate the burden of liver disease, including NASH.[13]

Clinical profile

Resmetirom is a hormonal agonist that activates a receptor in the liver called thyroid hormone receptor beta (THR-β). People with NASH have reduced levels of THR-β receptor activity in the liver.[14]

Activating THR-β function may provide metabolic benefits related to treating NASH. These include reducing excess liver fat and specific lipids linked to the formation of fatty plaques in the arteries. In addition, THR-β may also reduce the proteins responsible for transporting fats and lipids in the blood.[15]

Trial results

The efficacy of resmetirom was evaluated in a Phase 3 study (MAESTRO-NASH). Most patients (95%) had moderate or advanced fibrosis. Patients received 80 or 100 mg of resmetirom, or placebo once daily. Results were measured in three ways:

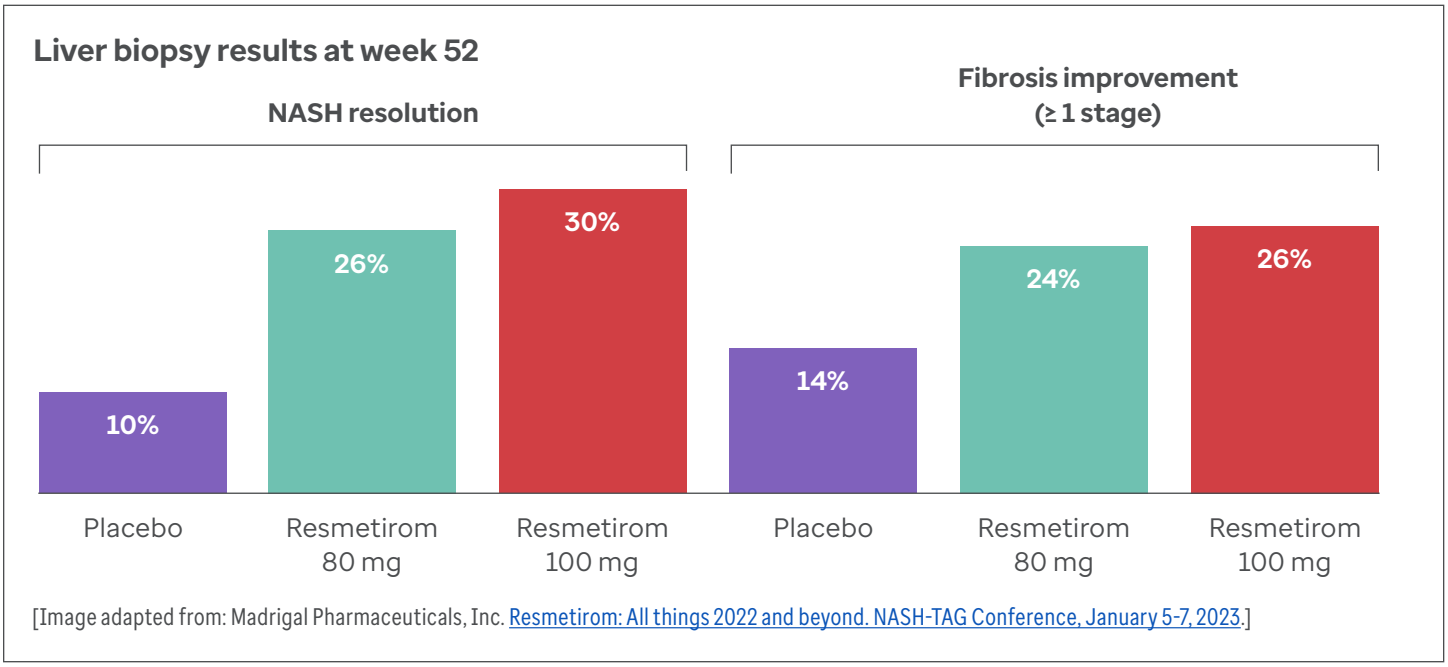
1. At least a 2-point reduction and with no worsening of fibrosis in a standardized biopsy test mainly used in clinical trials (NAFLD Activity Score).
2. A 1-point decrease in fibrosis with no worsening of the biopsy score after 52 weeks of treatment.
3. A key secondary endpoint was LDL cholesterol level.

Both the 80 mg and 100 mg doses of resmetirom met the primary goals of NASH resolution and no worsening of fibrosis on the standardized biopsy score. The results also showed a statistically significant lowering of LDL cholesterol.[16]

Resmetirom *(continued...)*

[Back to Contents]

This graph compares liver biopsy results at 52 weeks between the two dose sizes of resmetirom and placebo:



[Image adapted from: Madrigal Pharmaceuticals, Inc. Resmetirom: All things 2022 and beyond. NASH-TAG Conference, January 5-7, 2023.]

You can access an in-depth discussion of safety and trial data here (p. 9).

Competitive environment

Resmetirom is potentially the first FDA approved treatment for NASH.

The current first line treatment for NASH is lifestyle modification, primarily weight loss. A reduction in weight can reduce inflammation in the liver and potentially improve fibrosis. However, statistically few patients with NASH achieve adequate weight loss.

Off-label use of glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., semaglutide), insulin-sensitizing agents (e.g., pioglitazone), and vitamin E can be used in select patients, but the data for these therapies in NASH is limited, and none have been shown to improve fibrosis.

In June 2023, the FDA declined to approve Intercept Pharmaceuticals' obeticholic acid for NASH, based on efficacy and safety concerns. Unlike obeticholic acid, resmetirom met both of its dual primary efficacy endpoints and appears to have a better safety and tolerability profile.

The initial FDA approval decision for resmetirom is through the accelerated approval pathway. While the available efficacy data is promising, the outcomes are considered surrogate, that is, they are a substitute for a direct measure of how a patient feels, functions, or survives. A long-term outcomes trial is ongoing to evaluate actual clinical outcomes. This trial is not expected to be complete until the second half 2025.

Other drugs are currently under development for treatment of NASH, including GLP-1 receptor agonists such as tirzepatide and semaglutide. A Phase 3 trial for semaglutide is expected to complete sometime in 2025 and if positive, would be a potential competitor to resmetirom.

Aside from treatments, diagnosis is important for fatty liver diseases, like NASH. Currently, the gold standard for diagnosis is a liver biopsy, but biopsies are invasive, inconvenient, uncomfortable, and even dangerous.[17]

Biopsies are also impractical to deal with the scale of liver disease – perhaps as many as 60 million adults in the U.S. could need one. These limitationsrestrict everything from treatment to research on potential treatments.[18]

Therefore, it's worth noting that non-invasive diagnostics for liver disease is an active area of development. These include enhanced imaging procedures and blood tests, and would avoid the need for liver biopsies, and could influence the ease of diagnosis of NASH and uptake of resmetirom.[19]

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Unless otherwise specified, all citation taken from RxOutlook® 4th Quarter 2023.

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